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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JUAN MIGUEL JIMENEZ MAYORGA,
LAURA VIDAL GISPERT, and GRAHAM WARRELLOW

Appeal 2010-012157
Application 10/555,286
Technology Center 1600

Before TONI R. SCHEINER, ERIC GRIMES, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

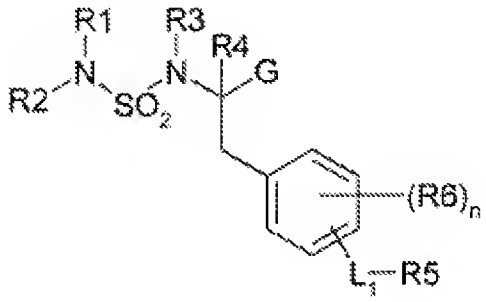
This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-10, 20, and 21, directed to N-(2-phenylethyl)sulfamide derivatives, which are antagonists of the α4 integrins. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

The present invention relates to "N-(2-phenylethyl)sulfamide derivatives . . . [which] are antagonists of the α4 integrins, both the α4β1 integrin (VLA-4, "Very Late Antigen-4" or CD49d/CD29) and/or the α4β7 integrin (LPAM-1 and α4βp)" (Spec. 1).

Claim 1, reproduced in its entirety in the Claims Appendix accompanying Appellants' Brief, is directed, in relevant part, to a compound of formula (I),



(I)

According to their Appeal Brief, Appellants elected the product of Example 11 (pictured below) for examination (App. Br. 14), and it is our understanding that the claims have been examined only to the extent they read on the elected species.

The Examiner rejected claims 1-10, 20 and 21 under 35 U.S.C. § 103(a) as unpatentable over Fukui[1] and Patani.[2]

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[1] International Patent Application No. WO 02/14272 A1 by Hideto Fukui et al., published February 21, 2002 (English translation).
[2] George A. Patani and Edmond J. LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, 96 CHEM. REV. 3147-3176 (1996).

OBVIOUSNESS

The Issue

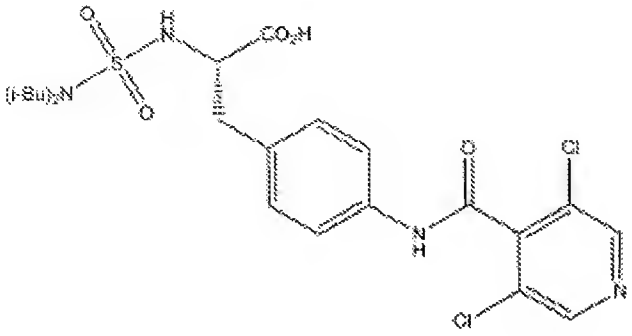
The Examiner finds that Fukui describes an antagonist of α4 integrin with a structure identical to the elected species, except that Fukui's compound has a carbonyl group where the claimed compound has a sulfone group (Ans. 3-4). The Examiner concludes that it would have been obvious to replace the carbonyl group of Fukui's compound, in order to make another α4 integrin antagonist, because Patani teaches that "sulfone (SO2) is a bioisostere of the carbonyl group" (*id.* at 4).

Appellants contend, among other things, that Patani's teachings would not have led one of ordinary skill in the art to replace the carbonyl group in Fukui's compound with a sulfone group, at least in part because Patani's specific examples show a decrease in activity when a carbonyl group was replaced by a sulfone group.

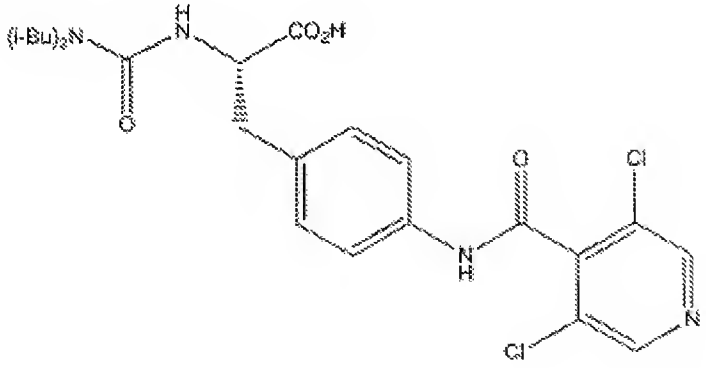
The issue raised by this appeal is whether the Examiner has established that it would have been obvious for one of ordinary skill in the art to modify Fukui's structurally similar compound in the specific manner required to achieve the claimed compound.

Findings of Fact

1. Appellants elected the following α4 integrin antagonist, which corresponds to Example 11 of the Specification, for examination on the merits:



2. Fukui discloses "(thio)urea derivatives . . . that are useful as VLA-4 antagonists" (Fukui, 3 of the translation). Fukui also discloses the following compound, which corresponds to its Working Example 4, and was one of 24 compounds tested for activity as α4 integrin antagonists:



Fukui's compound 4 was found to have an IC_{50} of 4.7 nM, as shown in Fukui's Table 6 below, which depicts the 50% inhibition concentration of the various compounds tested:

Table 6

Working Example	50% inhibition concentration (nM)
1	1.1
2	2.7
3	2.1
4	4.7
5	88
6	52
7	20
8	3.7
9	15
10	1.1
11	8.3
12	78
13	89
14	35
15	0.614
16	2.0
17	1.1
18	99
19	3.0
20	0.54
21	3.7
33	47
36	25
34	47

There are eleven compounds with IC_{50}s more favorable than compound 4, and twelve with less favorable IC_{50}s.

3. There is no dispute that Fukui's compound and Appellants' elected compound differ only in the substitution of a sulfone group for a carbonyl group.

4. According to Fukui, its (thio)urea derivatives (i.e., where the urea carbonyl group can also be a thiourea group) "exhibit outstanding VLA-4 antagonism" (Fukui, 24 of the translation).

5. Patani teaches that "[b]ioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents" (Patani 3147).

6. Patani teaches that "sulfoxides and sulfones are recognized as nonclassical bioisosteres suitable for replacement of a carbonyl group, [while] thioethers . . . are not" (Patani 3167).

7. Patani's Table 39 shows the effect of replacing the carbonyl group on the Leukotriene B_4 (LTB_4) receptor antagonist with a variety of polar and nonpolar bioisosteres:

Table 39. Receptor Affinity of LTB_4 Receptor Antagonists with Modified Linking Groups

compound	X	percent inhibition of specific [^{3}H]LTB_4 binding (μM)
82a	C=O	85
82b	C=NOH	84
82c	(C=O)NH	73
82d	S	67
82e	SO	71
82f	SO_2	79

Table 39 shows that sulfone bioisostere (82f) has somewhat lower inhibitory activity than the carbonyl bioisostere (82a).

Patani suggests that "the lack of any significant difference in activity upon replacement of the carbonyl with either a thioether, sulfoxide or sulfone, which differ widely with respect to their polarities and hybridization, suggests that this portion of the molecule is not critically involved in LTB_4 receptor binding" (Patani 3167).

8. Patani's Table 41 shows the activity of various ketone bioisosteres of a euglycemic compound:

Table 41. Euglycemic Activity of Various Ketone Isosteres

compound	X	dose (mg/kg)	% glucose normalization in ob/ob mouse[a]
85a	$CH_2C{=}O$ (CP-86,325)	1	100
85b	CH_2SO_2	5	69
85c	CONH	5	64
85d	$CH_2C(NOH)$	5	100
85e	$CH_2C(NOMe)$	5	100

[a] Ciglitazone was dosed at 50 mg/kg as a positive control and results are reported as the percentage of glucose normalization compared to the standard ciglitazone-treated group (100% at 50 mg/kg) and the vehicle treated group (0%).

Again, the sulfone bioisostere (85b) had lower activity than the carbonyl bioisostere (85a).

Principles of Law

"[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). Thus, in order to establish a prima facie case of obviousness, there must be "a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'" *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007), quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). That is, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda*, 492 F.3d at 1357.

Discussion

This is a close case. We agree with the Examiner that it would have been obvious for one of ordinary skill in the art to select Fukui's compound "as a reasonable lead for further modification" (Ans. 6) because it is one of a mere 24 compounds for which IC_{50} data is provided, and it exhibits good activity relative to the other compounds in that small group.

Nevertheless, having considered all the evidence of record, we are not persuaded that Patani's general teaching that "sulfoxides and sulfones are recognized as nonclassical bioisosteres suitable for replacement of a carbonyl group" (Patani 3167; FF6) would have led one of ordinary skill in the art make the specific substitution required by the claims, i.e., to replace the urea carbonyl group in Fukui's compound with a sulfone.

In the two specific examples disclosed by Patani, replacement of a carbonyl group with a sulfone resulted in decreased bioactivity (Patani 3167-68; Tables 39 and 41; FFs 7, 8), while other substitutions were somewhat more promising. More important, however, is Patani's comment that "the lack of any significant difference in activity upon replacement of the carbonyl [on the LTB_4 receptor antagonists shown in Table 39] with either a thioether, sulfoxide or sulfone, which differ widely with respect to their polarities and hybridization, suggests that this portion of the molecule is not critically involved in LTB_4 receptor binding" (Patani 3167; FF7).

Fukui, on the other hand, emphasizes that its (thio)urea derivatives (i.e., where the urea carbonyl group can also be a thio urea group) "exhibit outstanding VLA-4 antagonism" (Fukui, 24 of the translation; FF4), suggesting that the site at issue here is involved in the VLA-4 antagonistic

activity of its compounds. In our view, one of ordinary skill in the art would have considered it important to have a (thio)urea group in that position to maintain VLA-4 antagonism, outweighing Patani's generic teaching that sulfoxides and sulfones are bioisosteres suitable for replacement of a carbonyl group.

SUMMARY

The rejection of claims 1-10, 20, and 21 under 35 U.S.C. § 103(a) as unpatentable over Fukui and Patani is reversed.

REVERSED

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